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의학 석사 학위논문

췌관선암 주변 림프절에 대한 종양의 직접 침윤이 환자의 생존결과에 미치는 영향

Peritumoral lymph nodes in pancreatic cancer revisited; is it truly metastatic?

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서울대학교 대학원
의학과 외과학 전공
변 윤 형

Abstract

Peritumoral lymph nodes in pancreatic cancer revisited; is it truly metastatic?

Yoonhyeong Byun
Department of Surgery
Seoul National University

Background Lymph node (LN) metastasis is well-known to negatively affect the prognosis of pancreatic cancer. LN metastasis through direct invasion of tumor cell to peritumoral lymph nodes (PTLN) are treated as the same as those which spread through lymphatic channels. Previous studies were based on small number of cases without definitive conclusions. This study aimed to evaluate the impact of PTLN invasion on the oncologic outcome of pancreatic cancer.

Methods Medical records of 506 patients who received radical resection for pancreatic ductal adenocarcinoma from January 2012 to December 2018 were reviewed. Pathologic review was performed by one experienced pathologist. PTLN invasion was defined as a direct invasion of tumor cells in contact with main tumor.

Results Of the 506 patients, 176 (34.8%) were N0, 237 (46.8%) were N1, and 93 (18.3%) were N2. One-hundred twelve patients (22.1%) had PTLN invasion. In N1 stage, PTLN invasion group (PTLNI) had a significantly better 2- year survival than regional LN metastasis group (RLNM) and combined LN metastasis group (CLNM) (PTLNI 73.8% vs. RLNM 47.0% vs. CLNM 45.7%, p=0.006). There was no significant difference between N0 and PTLNI (PTLNI 73.8% vs. N0 69.4%, p=0.483). In multivariate analysis, the PTLNI was found to be a better prognostic factor (Hazard ratio 0.322 [0.182-0.570], p<0.001).

Conclusion Because PTLN invasion does not adversely affect survival as LN metastasis, pancreatic cancer can be over-staged if it were dealt like metastatic LN. Therefore, PTLN invasion should be disregarded from current nodal staging system.

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Keywords : peritumoral lymph node; direct invasion; pancreatic ductal adenocarcinoma; lymph node metastasis

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I. Introduction

Pancreatic cancer is well known for its devastating survival outcomes. Recently released statistics in the US show that it is the 4th leading cause of cancer death in both male and female.[1,2] One of the major reasons for such outcome is its tendency for early metastasis through the lymphatic drainage.[3,4] Many studies have demonstrated the adverse effect of lymph node (LN) metastasis.[5-9] Thus, the importance of accurately reporting the LN status cannot be overemphasized for proper staging and more accurate prognosis prediction.[10,11]

Various methods have been proposed in reporting LN status including simple presence of LN metastasis, number of metastatic LN, LN ratio, and log odds of positive LN.[9-17] The number of metastatic LN is the most commonly used reporting method and its significance has been externally validated.[13,15-20] The eighth edition of American Joint Committee on Cancer (AJCC) staging system adopted this method and now subcategorizes the N category according to the number of metastatic lymph nodes.[21] The basic premise of this quantitative assessment of LN by the AJCC staging system is that all regional LN metastasis have equal qualitative impact on the survival outcome of the pancreatic cancer.

Conceptually, there may be two different ways of LNs. One is by the lymphatic channel, and the other is by direct invasion of tumor to the adjacent LN. The former, with little to discuss, is a true metastatic LN. On the other hand, the latter can be considered as an invasion of

tumor cells rather than a true metastasis; thus, it can be called as peritumoral lymph node (PTLN) invasion. Studies on direct invasion of PTLN in other malignancies have already been conducted long ago.[22,23] However in pancreatic cancer, it is not yet well-documented whether these LN metastases of two different spreading methods have the same prognostic significance.

To assess the significance of the qualitative extent of LN metastasis, this study aimed to evaluate the impact of PTLN invasion on the survival outcome of pancreatic cancer patients and to compare it with the LN metastasis by lymphatic drainage.

II. Methods

Selection criteria for study patients

After acquisition of approval from Institutional Review Board of Seoul National University Hospital (IRB number H-1907-015-1044), medical records of 754 patients who received radical resection for pancreatic tumor from January 2012 to December 2018 were reviewed. Fifty-seven patients diagnosed with other histology than pancreatic ductal adenocarcinoma (intraductal papillary mucinous neoplasm, adenosquamous cell carcinoma, acinar cell carcinoma, neuroendocrine tumor, mucinous carcinoma, etc.), 59 patients who had R2 resections, 127 patients who received neoadjuvant treatment, 3 patients who

underwent additional pancreatectomy for metachronous pancreatic cancer in remnant pancreas, 1 patient whose LN was not assessed, and 1 patient who had multifocal lesions in both head and tail of the pancreas were excluded. Finally, 506 patients were eligible for analysis.

Pathologic review of specimens

Pathologic reports of the patients were reviewed, and those with one or more LN metastasis had their pathology reviewed by a pathologist specializing in pancreas (Kyung-bun Lee). The PTLN invasion (PTLNI) was defined as LN metastasis by direct invasion of the tumor into the adjacent LNs . Regional LN metastasis (RLNM) was defined as LN metastasis to regional LNs that were not in contact with the main tumor. (Fig. 1) The eighth edition of AJCC staging system was used for TNM staging in this study.

Grouping of the study patients

Study patients were categorized by the pattern of LN metastasis. Those without any PTLNI or RLNM were categorized as N0, and those with either PTLNI or RLNM were categorized as LNM+. The LNM+ group were subdivided into the following 3 subgroups; those with PTLN invasion alone (PTLNI group), those with RLNM alone without PTLN invasion (RLNM group), and those with combined LN metastasis of both PTLNI and RLNM (CLNM group).

Statistical analysis

Before comparing the survival outcome, demographics were compared between the groups and the subgroups. Survival analysis was done to compare the outcome of PTLNI group to those of RLNM and CLNM groups, and to that of N0 group. The N1 were selected for analysis to eliminate the possibility of bias due to high number of N2 in RLNM and CLNM when PTLNI group was compared to RLNM and CLNM groups.

For comparisons between two groups, Student's t-test was used for continuous variables with normal distribution and Mann-Whitney test was used for continuous variables without normal distribution or nonparametric variables. For comparisons between three or more groups, ANOVA was used for continuous variables with normal distribution, and Kruskal-Wallis test was used for continuous variables without normal distribution or nonparametric variables. Chi-square test was used to compare the categorical data. Multivariate analysis was performed on the factors that were significantly identified in the univariate analysis to determine the factors affecting the survival outcome in overall and in LN positive patients. The values of survival duration were calculated from the date of operation. Kaplan-Meier curves were plotted for presenting the survival results. The log-rank method was used for comparison of the results of the subgroups. Cox's proportional hazards model was used to determine the combined effects of factors affecting the survival outcome. Any p-value of less

than 0.05 was considered statistically significant.

III. Results

Overall clinicopathologic characteristics of patients

Of the 506 patients, 299 (59.1%) were male and the median age was 67 years. There were 314 patients (62.1%) with primary lesion located in pancreatic head, and 419 patients (82.8%) with R0 resection. Adjuvant chemotherapy and radiotherapy was given to 368 (72.7%) and 249 (49.2%) patients, respectively. In pathologic examination, T2 was the most common among the T category (325 patients, 64.2%) followed by T3, T1, and T4. Of the 330 patients with LN metastasis, 176 cases (34.8%) were N0, 237 (46.8%) were N1, and 93 (18.3%) were N2. (Table 1). The median follow-up period was 17 (9-29) months, the median overall survival was 27 months, and the 5-year survival rate was 24.7%.

Comparison by LN metastasis type

Metastatic LN was present in 330 patients (65.2%). Of the 330 patients, PTLN invasion was found in 112 patients (22.1%); 48 patients had PTLN invasion alone (PTLNI group) and 64 patients had both PTLN invasion and regional LN metastasis (CLNM group). The remaining 218 patients had only regional LN metastasis (RLNM group) as shown in Fig. 2.

Between the 3 subgroups of LN metastasis, there was no significant differences in the clinicopathologic features except for the distribution of sex and N stage (Table 1). There were significantly higher distributions of N2 stage in the CLNM and the RLNM groups compared to the PTLNI group (PTLNI 2.1%, CLNM 51.6%, RLNM 27.1%, $p<0.001$). Since this may have a significant effect on the comparison of survival outcomes between the groups, further correlation analysis between three groups was performed on patients without N2 cases. After excluding N2 cases, there still was no statistically significant difference between the groups in all clinicopathologic features other than sex (Table 2). Despite the similar clinicopathologic features, there were significant differences in survival outcomes. Within the N1 cases, CLNM and RLNM groups showed a 2-year survival rate (2-YSR) of 45.7% and 47.0%, respectively ($p=0.775$). The 2-YSR for PTLNI group was 73.8%. The survival outcome of PTLNI group was marginally better than CLNM group ($p=0.051$) and significantly better than RLNM group ($p=0.001$). (Fig. 3a).

Comparison between N0 and PTLN invasion

Compared to N0, PTLNI group showed more frequent R1 resection (22.9% vs. 11.4%, $p=0.039$), angiolymphatic invasion (50.0% vs. 28.4%, $p=0.005$), venous invasion (50.0% vs. 33.5%, $p=0.028$), and perineural invasion (93.8% vs. 76.7%, $p=0.004$) (Table 1). Regarding the T category, PTLNM group had significantly more advanced T category

(T1: 8.3% vs. 27.8%; T2: 62.5% vs. 61.4%; T3: 22.9% vs. 9.1%; T4: 6.3% vs. 1.7%; p=0.002).

The survival outcome was not significantly different between N0 and PTLNI (p=0.483). The median survival duration for N0 was 53 months and that of PTLNI was not achieved. The 2-year survival rates were 69.4% and 73.8% for N0 and PTLNI, respectively (Fig. 3b).

The role of PTLN invasion in the N1 and N2 category

Survival outcome was compared for N1 and N2 category with regards to regional LN metastasis alone and disregarding all the LNs with PTLN invasion. There were 159 N1s, 50 N1s with additional PTLNI (N1+PTLNI), 59 N2s, and 14 N2s with additional PTLNI (N2+PTLNI). There were no significant differences in median survival duration between N1 and N1+PTLNI (23 months vs. 23 months, p=0.612) and between N2 and N2+PTLNI (16 months vs. 15 months, p=0.829). However, there also was no significant difference between N1+PTLNI and N2 (23 months vs. 16 months, p=0.159) as depicted in Fig. 4a.

However, there was a significant difference between N1 with or without PTLNI (n=209) and N2 with or without PTLNI (n=73) with median survival of 23 months and 15 months, respectively (p=0.021, Fig. 4b).

PTLN invasion as a prognostic factor

Multivariate analysis was performed on clinicopathologic features that were significantly associated with overall survival in univariate analysis (Table 3). Adjuvant chemotherapy (HR 0.506 [95% CI 0.385-0.664], $p<0.001$), adjuvant radiotherapy (HR 0.635 [95% CI 0.491-0.821], $p<0.001$), poorly differentiated histologic grade(HR 1.943 [95% CI 1.382-2.731], $p<0.001$), presence of angiolymphatic invasion (HR 1.403 [95% CI 1.078-1.827], $p=0.012$), venous invasion (HR 1.364 [95% CI 1.050-1.771], $p=0.020$), perineural invasion (HR 1.753 [95% CI 1.128-2.724], $p=0.013$), T3 or above (HR 1.466 [95% CI 1.102-1.949], $p=0.009$), presence of LN metastasis (HR 1.772 [95% CI 1.296-2.422], $p<0.001$), and PTLN invasion only (HR 0.327 [95% CI 0.185-0.580], $p<0.001$) were independent prognostic factors in total population. In patients with LN metastasis, similar results were found with the exception of T3 or above. The PTLN invasion only group showed a significantly better prognosis compared to other groups (HR 0.301 [95% CI 0.169-0.537], $p<0.001$).

IV. Discussion

While quantitative evaluation of LN metastasis has been well-documented, there are no sufficient reports on qualitative measure of LN metastasis.[7,9,13,16,17] One of the aspects of qualitative LN metastasis is the metastasis to PTLNs. Given that tumor cells are

found in PTLN with continuity to the main tumor suggesting direct invasion, should this be considered as LN metastasis or simply as an extension of the main tumor?

Several studies have investigated the effect of PTLN invasion on the prognostic outcome.[24-28] The first study in the literature on PTLN was published in 2010 by Massachusetts General Hospital group.[24] They reviewed 517 patients who underwent pancreatic resection for PDAC and found direct invasion in at least 20% of patients with 1 or 2 lymph node metastases. There was no statistically significant difference in the median overall survival of 32 patients with PTLN invasion and 131 patients with regional LN metastasis (p=0.67). Thus, they concluded that the pattern of LN metastasis had no effect on the prognosis. Pai et al.[25] reviewed 380 patients with T3 pancreatic ductal adenocarcinoma at two centers and reported that 35 (9.2%) patients had PTLN invasion. They found no statistically significant difference between 97 N0 patients and 35 PTLNI patients (median survival; 30 vs. 21 months, p=0.609); however, they found significant difference between the PTLNI patients and 248 standard N1 patients (21 vs. 15 months, p=0.001). No conclusion can be drawn from these studies not only because of the conflicting results but also due to several other shortcomings. These studies are limited to observing patients with PTLN invasions in 1 or 2 LNs. Moreover, these two studies cover long periods of time extending from the 1990s to 2000s during which dramatic changes in pancreatic cancer treatments were made.

One of the strong points of the current study is that the pathology was fully reviewed for all LN metastasis cases by a single pancreas-dedicated pathologist. Most patients with PTLN invasion had 3 or fewer metastatic lymph nodes, and only one patient had invasion into 5 PTLNs. The prevalence of PTLN invasions was 22.1% of patients, and that of PTLN invasion alone without LN metastasis was 9.5%.

To determine whether the prognostic impact of PTLN invasion differs from other regional lymph node metastasis through lymphatic channel, PTLNI was compared with other types of LN metastasis. While they have similar clinicopathologic characteristics, the survival outcome of PTLNI group was significantly superior to those of RLNM or CLNM groups as demonstrated in Fig. 3a. Thus, PTLN invasion alone is a distinct group and displays better prognosis compared to regional LN metastasis. Therefore, in patients with PTLNI alone, there is a question about whether this should be considered as a true lymph node metastasis, which can affect survival outcomes like other lymph node metastasis.

The next question is how PTLNI patients differ from N0 patients. A French study of 306 patients (35 PTLNI patients) from a single institution concluded that although PTLN invasion demonstrates significantly worse outcome compared to N0, it had less impact on the survival outcome compared to the regional LN metastasis.[26] However, this study included patients with intraductal papillary mucinous

neoplasm with invasive carcinoma. Another study from UCLA with 385 patients showed no difference between PTLNI alone and N0 (51.8 vs. 40.7 months, p=0.815). However, it was limited by having only 14 PTLNI patients.[27] In a Japanese single institution study of 98 PDAC patients, PTLNI was found in 27 (27.6%) patients.[28] They reported that there was no statistically significant difference in survival outcomes between patients with PTLNI and patients without LN metastasis. The current study demonstrated that PTLNI group had similar survival outcome compared to N0 patients in terms of median survival duration and 2-year survival rate. Based on these observations, it can be said that PTLN invasion without any other LN metastasis is a different entity from LN metastasis through lymphatic channels and shares similar prognosis with N0 state.

Whereas PTLN invasion had no effect on survival without regional LN metastasis, its effect in the presence of regional LN metastasis was uncertain. While there were no differences in survival whether or not there were additional PTLN invasion for each N1 and N2 (p=0.612 and p=0.829), there was also no difference between N1 with PTLNI and N2 (p=0.159). There was a difference when grouped as N1 and N2 disregarding PTLN invasion (p=0.021). Up to date, there are no reports concerning the role of PTLN invasion in N1 and N2 diseases; and the result in the current study was inconclusive. Therefore, conclusion regarding the effect of PTLN in N1 and N2 disease cannot be drawn and warrants further study with increased population.

Lastly, PTLN invasion alone was found to have better survival in multivariate analysis of clinicopathologic features. Furthermore, its enhanced prognosis is accentuated when compared within the LN metastasis group (Table 3). Thus, PTLN invasion alone is an independent prognostic factor. Cases with PTLN invasion only should not be regarded as LN metastasis, but rather as N0 cases. Considering its significance in multivariate analysis, distinguishing PTLN invasion alone from LN metastasis should be considered in staging patients.

This study has several limitations. First, it is a retrospective study, which seem inevitable since LN metastasis or invasion cannot be controlled. However, to increase the credibility, the slides of all LN positive cases were reviewed by an expert pathologist. Nevertheless, it is impossible to rule out the possibility that any bias caused by confounding factors had acted on the results of this study. Secondly, the number of PTLNI group was not as large as desired but it is the largest cohort of PTLNI group to our knowledge. Finally, the effect of PTLN invasion in N2 could not be investigated due to limited number of patients with PTLN invasion into 4 or more LNs.[24,25] Further studies including multi-institutional or meta-analysis may be helpful to further overcome these Limitations.

In conclusion, patients with direct invasion of tumor cell to PTLN without other LN metastasis have superior outcome compared to those with LN metastasis through lymphatics. Furthermore, these set of patients have similar or slightly better outcomes than N0 patients. The

PTLN invasion alone was an independent prognostic factor for pancreatic cancer. Therefore, Patients with PTLN invasion only should not be classified as N1. Since the current method of staging allows the possibility for over-staging in PTLNI patients, the future staging system should take PTLN invasion separately into account from other regional lymph node metastasis.

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Table 1. Clinicopathological distributions and comparisons by the types of metastatic lymph nodes

Variables	Total (n=506)	*LNM− (n=176)	†LNM+ (n=330)			*p*-value (‡PTLNI vs. ¶CLNM vs. §RLNM)	*p*-value (‡PTLNI vs. *LNM−)
			‡PTLNI (n=48)	¶CLNM (n=64)	§RLNM (n=218)		
Sex (Male, %)	299 (59.1)	107 (60.8)	32 (66.7)	27 (42.2)	133 (61.0)	0.012	0.285
Age (Mean±‖SD)	65.9 ± 9.6	66.0 ± 10.5	65.3 ± 10.9	66.4 ± 8.7	65.8 ± 8.9	0.807	0.709
Location (Head, %)	314 (62.1)	99 (56.3)	30 (62.5)	42 (65.6)	143 (65.6)	0.917	0.271
R0 resection (%)	419 (82.8)	156 (88.6)	37 (77.1)	52 (81.3)	174 (79.8)	0.861	0.039
Adjuvant Chemotherapy(%)	368 (72.7)	121 (68.8)	36 (75.0)	46 (71.9)	165 (75.7)	0.826	0.257
Adjuvant Radiotherapy (%)	249 (49.2)	87 (49.4)	24 (50.0)	25 (39.1)	113 (51.8)	0.197	0.537
Histologic grade (%)						0.815	0.949
Well	54 (10.7)	21 (11.9)	5 (10.4)	4 (6.3)	24 (11.0)		
Moderate	384 (75.9)	132 (75.0)	37 (77.1)	52 (81.3)	163 (74.8)		
Poorly	68 (13.4)	23 (13.1)	6 (12.5)	8 (12.5)	31 (14.2)		
T stage (%)						0.988	0.002
T1	76 (15.0)	49 (27.8)	4 (8.3)	4 (6.3)	19 (8.7)		
T2	325 (64.2)	108 (61.4)	30 (62.5)	43 (67.2)	144 (66.1)		
T3	87 (17.2)	16 (9.1)	11 (22.9)	14 (21.9)	46 (21.1)		
T4	18 (3.6)	3 (1.7)	3 (6.3)	3 (4.7)	9 (4.1)		
N stage (%)						<0.001	<0.001
N0	176 (34.8)	176 (100.0)	0	0	0		
N1	237 (46.8)	0	47 (97.9)	31 (48.4)	159 (72.9)		
N2	93 (18.4)	0	1 (2.1)	33 (51.6)	59 (27.1)		
**ALI (%)	251 (49.6)	50 (28.4)	24 (50.0)	43 (67.2)	134 (61.5)	0.175	0.005
†† VI (%)	252 (49.8)	59 (33.5)	24 (50.0)	39 (60.9)	130 (59.6)	0.427	0.028
‡‡ PNI (%)	441 (87.2)	135 (76.7)	45 (93.8)	59 (92.2)	202 (92.7)	0.950	0.004

*LNM−, absence of lymph node metastasis; †LNM+, presence of lymph node metastasis; ‡PTLNI, peritumoral lymph node invasion; ¶CLNM, combined lymph node metastasis; §RLNM, regional lymph node metastasis; ‖SD, standard deviation; **ALI, angiolymphatic invasion; †† VI, venous invasion; ‡‡ PNI, perineural invasion

Table 2. Clinicopathological comparisons by the types of metastatic lymph nodes in N1 stage

Variables	Total (n=237)	*PTLNI (n=47)	† CLNM (n=31)	‡ RLNM (n=159)	*p*-value
Sex (Male, %)	132 (55.7)	31 (66.0)	9 (29.0)	92 (57.9)	0.004
Age (Mean±¶SD)	65.7 ± 9.4	65.1 ± 10.9	65.6 ± 9.7	65.9 ± 8.9	0.857
Location (Head, %)	153 (64.6)	30 (63.8)	19 (61.3)	104 (65.4)	0.902
R0 resection (%)	187 (78.9)	36 (76.6)	24 (77.4)	127 (79.9)	0.869
Adjuvant Chemotherapy (%)	179 (75.5)	35 (74.5)	23 (74.2)	121 (76.1)	0.958
Adjuvant Radiotherapy (%)	124 (52.3)	23 (48.9)	15 (48.4)	86 (54.1)	0.738
Histologic grade (%)					0.919
Well	26 (11.0)	5 (10.6)	2 (6.5)	19 (11.9)	
Moderate	179 (75.5)	36 (76.6)	24 (77.4)	119 (74.8)	
Poorly	32 (13.5)	6 (12.8)	5 (16.1)	21 (13.2)	
T stage (%)					0.885
T1	24 (10.1)	4 (8.5)	3 (9.7)	17 (10.7)	
T2	157 (66.2)	29 (61.7)	23 (74.2)	105 (66.0)	
T3	46 (19.4)	11 (23.4)	4 (12.9)	31 (19.5)	
T4	10 (4.2)	3 (6.4)	1 (3.2)	6 (3.8)	
§ALI (%)	128 (54.0)	23 (48.9)	17 (54.8)	88 (55.3)	0.737
‖VI (%)	123 (51.9)	23 (48.9)	14 (45.2)	86 (54.1)	0.596
**PNI (%)	216 (91.1)	44 (93.6)	27 (87.1)	145 (91.2)	0.611

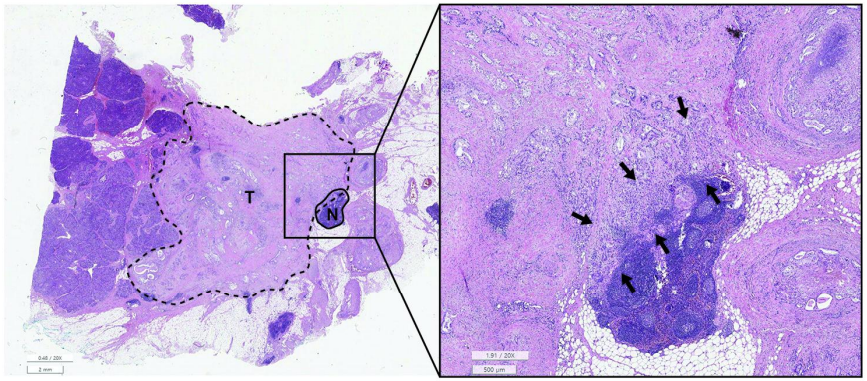
*PTLNI, peritumoral lymph node invasion; † CLNM, combined lymph node metastasis; ‡ RLNM, regional lymph node metastasis; ¶SD, standard deviation; §ALI, angiolymphatic invasion; ‖VI, venous invasion; **PNI, perineuralinvasion

Table 3. Univariate and multivariate analysis of factors affecting survival outcomes

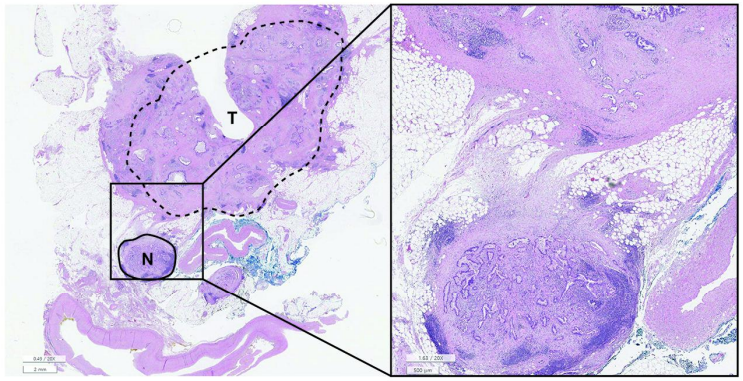
Factors	In overall						In *LNM+group					
	Univariate			Multivariate			Univariate			Multivariate		
	†HR	[95% ‡CI]	*p*-value	†HR	[95% ‡CI]	*p*-value	†HR	[95% ‡CI]	*p*-value	†HR	[95% ‡CI]	*p*-value
Sex: Female	0.906	[0.705 - 1.166]	0.444				0.932	[0.695 - 1.250]	0.640			
Age ≥ 66 years	1.026	[0.804 - 1.310]	0.838				1.107	[0.831 - 1.474]	0.487			
BMI ≥ 23 kg/m^2	0.805	[0.630 - 1.028]	0.082				0.835	[0.626 - 1.113]	0.219			
Location (Body/Tail)	0.702	[0.542 - 0.908	0.007	0.779	[0.597 - 1.017]	0.066	0.788	[0.580 - 1.070]	0.126			
R1 resection status	1.441	[1.058 - 1.962]	0.021	1.241	[0.902 - 1.708]	0.185	1.435	[1.015 - 2.030]	0.041	1.322	[0.929 - 1.882]	0.121
Adjuvant chemotherapy	0.612	[0.472 - 0.792]	<0.001	0.506	[0.385 - 0.664]	<0.001	0.449	[0.332 - 0.609]	<0.001	0.422	[0.308 - 0.578]	<0.001
Adjuvant radiotherapy	0.613	[0.478 - 0.786]	<0.001	0.635	[0.491 - 0.821]	0.001	0.531	[0.395 - 0.713]	<0.001	0.552	[0.407 - 0.748]	<0.001
Histologic grade: ¶PD	1.694	[1.216 - 2.361]	0.002	1.943	[1.382 - 2.731]	<0.001	1.629	[1.100 - 2.412]	0.015	1.777	[1.195 - 2.645]	0.005
Angiolymphatic invasion	1.803	[1.409 - 2.308]	<0.001	1.403	[1.078 - 1.827]	0.012	1.586	[1.176 - 2.138]	0.002	1.448	[1.068 - 1.963]	0.017
Venous invasion	1.788	[1.394 - 2.294]	<0.001	1.364	[1.050 - 1.771]	0.020	1.613	[1.191 - 2.185]	0.002	1.389	[1.015 - 1.901]	0.040
Perineural invasion	2.128	[1.397 - 3.243]	<0.001	1.753	[1.128 - 2.724]	0.013	1.999	[1.085 - 3.682]	0.026	1.800	[0.960 - 3.374]	0.067
T stage ≥ T3	1.743	[1.328 - 2.289]	<0.001	1.466	[1.102 - 1.949]	0.009	1.242	[0.910 - 1.696]	0.171			
LN metastasis	1.993	[1.510 - 2.630]	<0.001	1.772	[1.296 - 2.422]	<0.001						
§PTLN invasion only	0.488	[0.279 - 0.853]	0.012	0.327	[0.185 - 0.580]	<0.001	0.362	[0.206 - 0.636]	<0.001	0.301	[0.169 - 0.537]	<0.001
N2 stage	2.137	[1.604 - 2.848]	<0.001	1.153	[0.829 - 1.604]	0.396	1.716	[1.265 - 2.329]	0.001	1.227	[0.880 - 1.711]	0.228

*LNM+, presence of lymph node metastasis; †HR, hazard ratio; ‡CI, confidence interval; ¶PD, poorly differentiated; §PTLN, peritumoral lymph node

Figure 1. Comparison of histologic findings between direct invasion of peritumoral lymph node and metastatic regional lymph node (In the low-magnification images on the left side of A and B, the portion indicated by "T" is the main pancreatic cancer lesion, and its boundary is indicated by a dotted line. The portion indicated by "N" is a lymph node, and its boundary is indicated by a solid line.) (A) Contiguous extension of tumor cells from the tumor to peritumoral lymph node is observed (Indicated by arrows), indicating peritumoral lymph node invasion rather than metastasis. (hematoxylin-eosin stain, x4.8, x19.1) (B) There is no continuity between tumor and the metastatic peripancreatic lymph node. Hence, lymph node metastasis through lymphatics can be observed in regional lymph node metastasis. (hematoxylin-eosin stain, x4.9, x16.3).



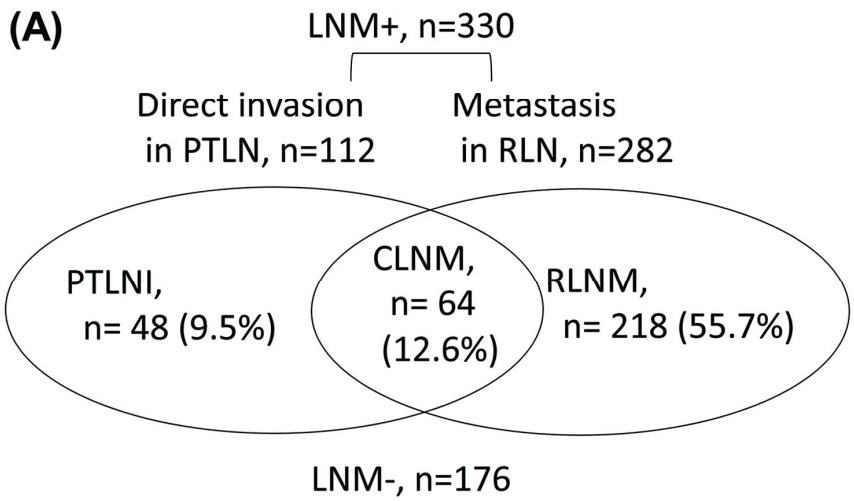
(A)



(B)

Figure 2. Distribution according to (A) the type and (B) the number of metastatic LN is illustrated.

(A)



(B)

		Metastasis in RLN					
		0	1	2	3	≥4	Total
Direct invasion in PTLN	0	176	87	50	22	59	394
	1	27	15	12	5	6	65
	2	14	3	2	2	4	25
	3	6	2	1	2	3	14
	≥4	1	2	2	2	1	8
	Total	224	109	67	33	73	506

Figure 3. (A) The comparison of overall survival of PTLNI group (no regional LN metastasis) and RLNM group and CLNM (regional LN metastasis with PTLN invasion) in N1 disease reveals distinct and superior outcome of PTLNI group. (B) PTLNI group has similar survival outcome with N0 patients.

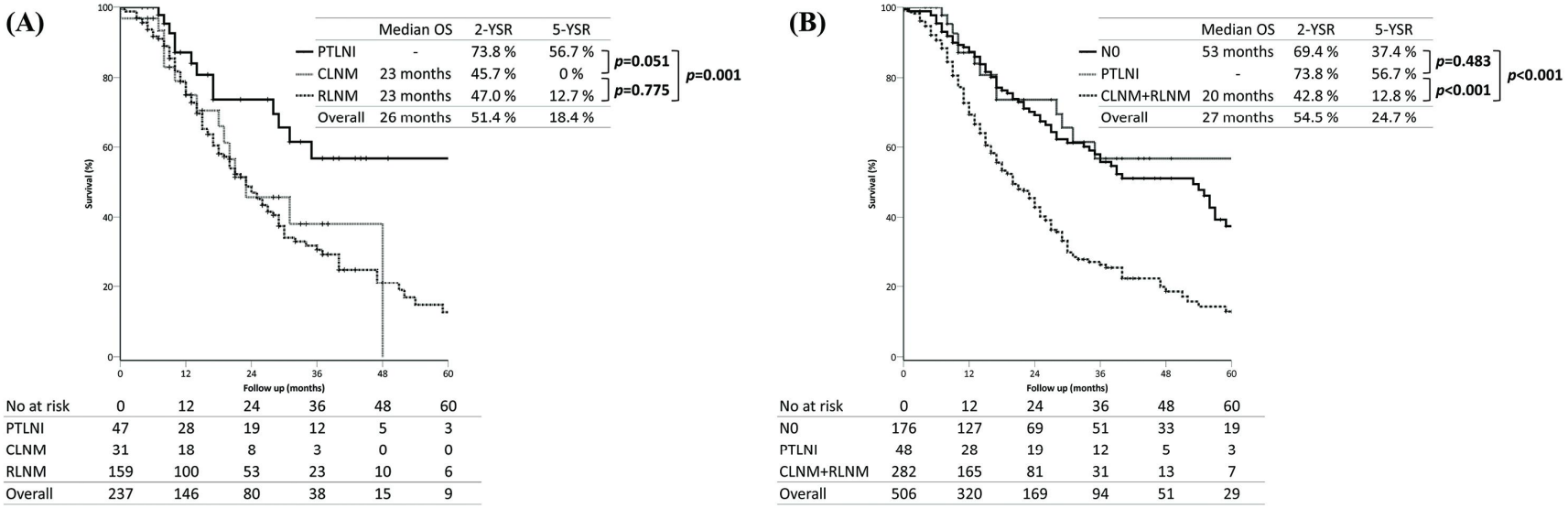
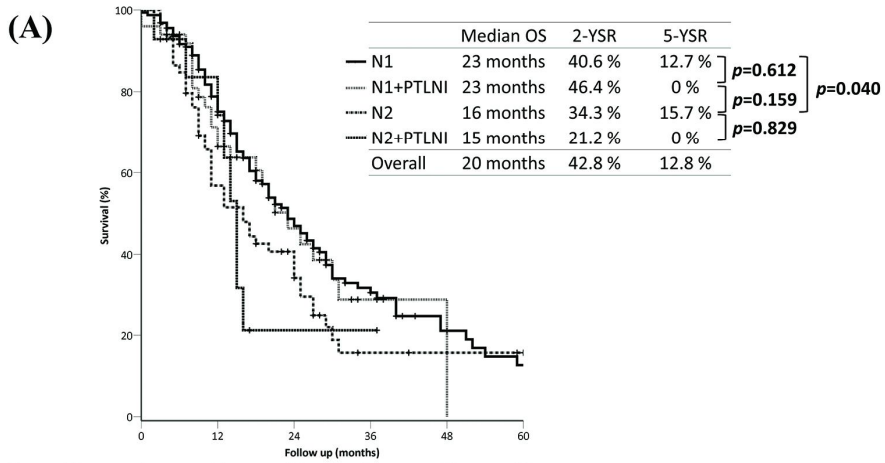
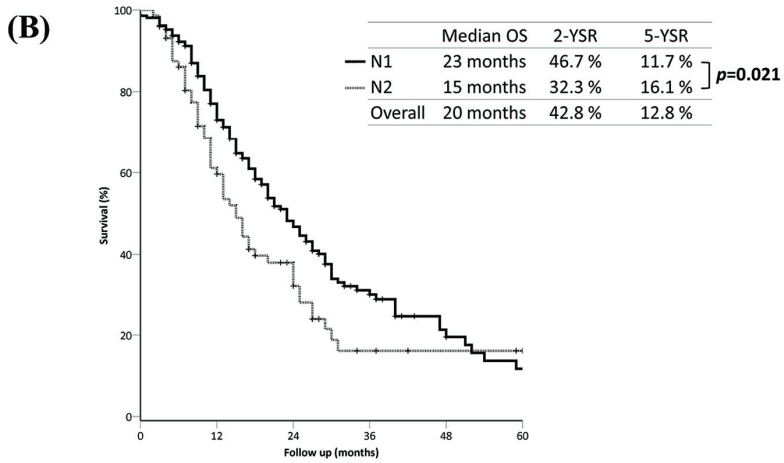


Figure 4. (A) Comparison of survival outcomes between subgroups of N1 without PTLNI, N1 with PTLNI, N2 without PTLNI, and N2 with PTLNI shows no significant intergroup differences. (B) Subgrouping into N1 and N2 disregarding the presence of PTLN invasion shows significant difference between groups (p=0.021).



No at risk	0	12	24	36	48	60
N1	159	100	53	23	10	6
N1+PTLNI	50	26	12	3	0	0
N2	59	32	15	4	3	1
N2+PTLNI	14	7	1	1	0	0
Overall	282	165	81	31	13	7



No at risk	0	12	24	36	48	60
N1	209	126	65	26	10	6
N2	73	39	16	5	3	1
Overall	282	165	81	31	13	7

국문초록

췌관선암 주변 림프절에 대한 종양의 직접 침윤이 환자의 생존결과에 미치는 영향

배경: 림프절 전이는 비교적 잘 알려진 췌장암의 예후 인자 중 하나이다. 이 중 종양 주변 림프절에 췌장암이 직접 침습하는 경우의 림프절 전이 형태는 림프절 채널을 통해 전이되는 다른 림프절의 전이와는 차이가 있음에도 불구하고 병기 설정이나 치료 방침에 있어서 똑같이 취급되고 있다. 이와 관련된 기존의 연구들은 연구의 대상자 수가 적거나 뚜렷한 결론을 내리지 못하고 있어 종양 주변 림프절의 직접 침습에 대한 종양학적 의미를 확인하기 위해 본 연구를 진행하였다.

방법: 본 연구는 2012년부터 2018년까지 서울대학교 병원에서 췌관선암으로 근치적 수술을 받은 506명의 환자를 대상으로 의무기록 검토를 통해 진행되었다. 환자 중 최종 병리 진단이 췌관선암이 아니거나 근치적 목적의 수술이 아닌 환자, 수술 전 항암화학치료를 받은 환자, 남은 췌장에 새로운 췌장암이 발병하여 추가 수술을 받은 환자, 림프절 절제가 이루어지지 않은 환자, 병변의 위치가 다발성인 환자는 분석에서 제외하였다.

결과: 전체 506명의 환자 중 림프절 병기 분포는 176명 (35%)이 N0, 237명 (47%)이 N1, 93명 (18%)이 N2인 것으로 나타났다. 이 중 112명 (22%)에서 종양 주변 림프절의 직접 침윤이 있는 것으로 나타났다. N1 병기 환자들에서, 종양 주변 림프절의 직접 침윤만 있는 환자들은 다른 림프절 전이가 확인된 환자 또는 두 가지 형태의 림프절 전이가 함께 동반된 환자에 비해 2년 생존율이 통계적으로 유의하게 더 나은 결과를 보였다 (2년 생존율: 종양 주변 림프절의 직접 침윤만 있는 경우 74%, 다른 림프절 전이만 있는 경우 47%, 두 가지 형태가 함께 동반된 경우 46%, p=0.006). 하지만, 림프절 전이가 없는 N0 환자와 종양 주변 림프절의 직접 침윤만 있는 환자의 생존율은 유의한 차이가 없었다 (종양 주변 림프절의 직접 침윤만 있는 경우 74%, 림프절 전이가 없는 경우 69%, p=0.483).

결론: 종양 주변 림프절의 직접 침윤은 다른 림프절 전이와 비교하여 생존 결과에 나쁜 영향을 미치지 않기 때문에, 이를 다른 림프절 전이와 똑같이 취급하는 현재의 췌장암 림프절 병기 시스템은 과장될 우려가 있다. 따라서 현재의 췌장암 림프절 병기에서 종양 주변 림프절의 직접 침윤은 따로 취급되어야 한다.

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주요어 : 종양 주변 림프절, 직접 침윤, 췌관선암, 림프절 전이
학 번 : 2018-22605